Reactions to Contrast Media According to Injection Time: Incidence and Clinical Characteristics

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排泄性尿路造影剤の注入時間から見た副作用

—頻度と臨床的特徴—

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九州大学医学部付属病院の排泄性尿路造影施行例のうち2,878例を対象として，造影剤の注入時間（注入開始から終了までに要した時間）と副作用の関係について検討した．イオタラム酸ナトリウムを81秒以上かけて静脈注射した群は，それ以下で注入した群より副作用の発現頻度が高かった．女性では，アミドトリゾ酸ナトリウム・メグルミンを7分以上かけて点滴注入した群は，他の群より副作用頻度が高かった．悪心あるいは嘔吐の発現頻度は，81～100秒で注入した群で低かった．血管痛の発現頻度は，1～20秒と41～60秒で注入した群で低かった．点滴注入した群では，悪心あるいは嘔吐，血管痛の頻度に，注入時間による差は見られなかった．

蕁麻疹の原因は，悪心・嘔吐または血管痛の原因とは異なると考えられた．

副作用発現頻度からは，より安全な注入時間を決めることはできなかった．

Abstract

The relationships between injection times and acute reactions to contrast media were examined among 2,824 patients. During bolus injections of sodium iothalamate, injection times longer than 81 seconds resulted in a higher incidence of reactions than when the injections were relatively rapid. In females, the incidence of reactions was higher in the group whose injection times were more than 7 minutes to administer mixtures of meglumine amidotrizoate and sodium amidotrizoate via drip infusions. The incidence of nausea and/or vomiting was lower in the group whose injection times were 81 to 100 seconds. The incidence of vascular pain was lower in the group whose injec-

tion times were 1 to 20 seconds and 41 to 60 seconds than in other groups. The incidence of these reactions was similar with all injection speeds, using drip infusions. There is no relatively "safe" or "safer" injection time.

The cause of urticaria is different from that of nausea and/or vomiting, or vascular pain.

During excretory urography and contrast-enhanced computed tomography, reactions of varying intensity to contrast media can occur, the etiology of which remain obscure. They cannot be attributed to a single cause. Reactions are categorized as due to true allergy or hypersensitivity (1–3), chemotoxia (4, 5), contrast-induced histamine release (6–8), hypertonicity (9, 10), activation of complement and coagulation sequences (11–13), and anxiety (14). No matter the cause, if there were a relatively "safe" injection time for a contrast medium, all radiologists would be bound to inject that contrast medium in that time.

This study adds to the body of available data, observations of a large series of patients concerning the incidence and clinical characteristics of reactions to urographic contrast media. The relationships between injection times and acute reactions of contrast media were explored.

Subjects and Methods

From March, 1979 through August, 1980, 2,824 patients were referred to the Department of Radiology, Kyushu University Hospital, for excretory urography. There were 1,182 males and 1,642 females, ranging in age from infancy to 88 years. Injection times for, and reactions to, the contrast media they received were recorded, but the severities of their reactions were not recorded. Pretests consisted of the intravenous administration of 0.5–1.0 ml contrast media prior to urography. Prior to urography, patients were advised that they might experience a transient sense of warmth as a normal physiologic effect of the contrast medium injected.

For 1,244 urographic examinations a bolus injection of sodium iothalamate was used; for 1,427, a drip infusion of meglumine amidotrizoate (53%) and sodium amidotrizoate (8%). The remaining 153 received drip infusions of meglumine iodamide 64.9%. Adults received 40 ml sodium iothalamate, a 100 ml mixture of meglumine amidotrizoate and sodium amidotrizoate, and 100 ml meglumine iodamide. Children's doses ranged from 10 to 30 ml of the contrast medium mentioned above, depending on age, weight, and renal function.

Results were tested for statistical significance, and a level of $p<0.05$ was regarded significant.

Results

The over-all incidence of reactions was 8.5%, and equal in both sexes (Fig. 1). There were no deaths from urography, though prompt, vigorous treatment was required for 2 patients with hypotension and dyspnea. One of them received a bolus injection of 40 ml sodium iothalamate; the other, a 100 ml mixture of meglumine amidotrizoate and sodium amidotrizoate via drip infusion. In males, the mixture of meglumine and sodium amidotrizoate resulted in a lower rate of reactions than did other contrast media, with a statistically significant difference ($p<0.05$). In females, no significant difference in the incidence of reactions was observed among the three contrast media.

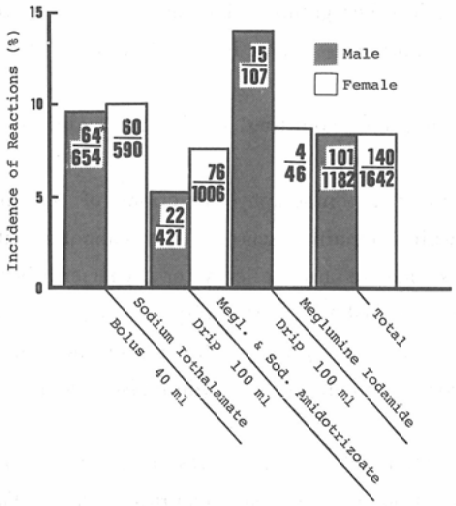

Fig. 1　Incidence of reactions to contrast media by sex and contrast media.

* No. of patients with reactions / No. of patients examined

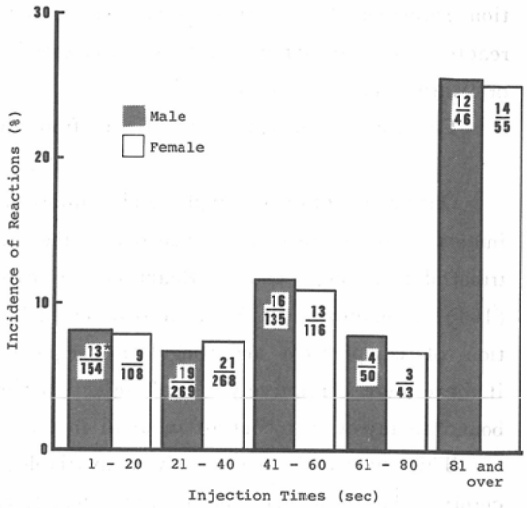

Fig. 2　Incidence of reactions to contrast media by injection time; sodium iothalamate bolus.

* No. of patients with reactions / No. of patients examined

There was no difference by sex for mixtures of meglumine amidotrizoate and sodium amidotrizoate. The causes of these differences by sex, type of contrast medium and incidence of reactions to contrast media were not determined. Most of the female patients were hospitalized in the Department of Gynecology, and they discussed among themselves reactions to contrast media before their examinations. Anxiety being one of the most important factors in producing reactions to contrast media (14), it might account for their results.

There was a higher incidence of reactions with injection times longer than 81 sec. when sodium iothalamate was administered. This difference was statistically significant ($p<0.001$) (Fig. 2). In females, the incidence of reactions was higher with injection times greater than 7 minutes than in other groups, using mixtures of meglumine amidotrizoate and sodium amidotrizoate (Fig. 3). We could not explain the relationship between injection times and acute reactions, there being few patients with reactions to meglumine iodamide.

The most commonly experienced reactions were nausea and/or vomiting, vascular pain and urticaria (Table I). The frequency of nausea and/or vomiting and vascular pain were higher with sodium iothalamate than with mixtures of meglumine amidotrizoate and sodium amidotrizate, or meglumine iodamide, with a statistically significant difference ($p<0.005$ and $p<0.001$). The rate of urticaria was lower with sodium iothalamate than with other contrast media ($p<0.001$). The frequency of nausea and/or vomiting was lower with injection times of 81 to 100 sec. using sodium iothalamate ($p<0.025$) (Fig. 4). Vascular pain was less frequent with injection times of 1 to 20 sec. and 41 to 60 sec., than with other injection times using sodium iothalamate ($p<0.025$) (Fig. 4). The frequencies of all reactions were similar at all injection times using mixtures of meglumine amidotrizoate and sodium amidotrizoate or meglumine iodamide (Fig. 5).

Table 1 Reactions to Contrast Media According to Injection Technique

Administration	Reactions (%)*			Patients with Reactions No. (%)
	Nausea and/or Vomiting	Vascular Pain	Urticaria	
Bolus Injection	71 (57.3)**	26 (21.0)°	17 (13.7)	124 (100)
Drip Infusion	43 (36.8)	7 (6.0)	49 (41.9)°°	117 (100)

* Some patients experienced more than one reaction.
** Statistically significant difference ($p<0.005$).
° Statistically significant difference ($p<0.001$).
°° Statistically significant difference ($p<0.001$).

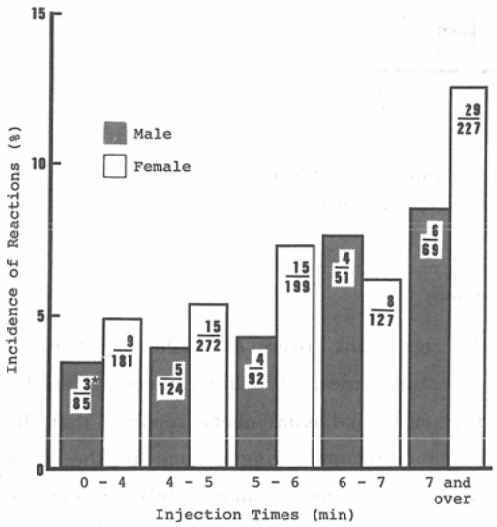

Fig. 3 Incidence of reactions to contrast media by injection time; mixture of meglumine amidotrizoate and sodium amidotrizoate drip.

* No. of patients with reactions / No. of patients examined

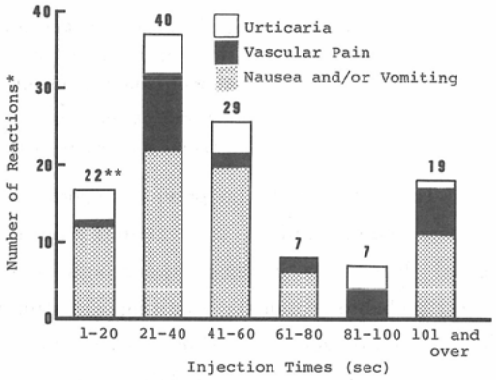

Fig. 4 Reactions according to injection times using bolus injections of sodium iothalamate.

*Some patients experienced more than one reaction.
**Total patients with reactions.

Discussion

Shehadi reported that injections within a few seconds to a minute were accompanied by lower reaction rates than were slower injections (15). In our series there was a lower rate of reactions with injections of 1 to 80 sec. than with injections lasting 81 seconds and more, using a bolus of sodium iothalamate. More frequent reactions with slow injections could result during the initial injection and subsequent prolonged injection. Nausea and/or vomiting and vascular pain sometimes occurred during the courses of injections. In our series, whereas nausea and/or vomiting were less frequent with slow bolus injections (81 to 100 sec.), vascular pain was less frequent with rapid bolus injections (1 to 20 sec. and 41 to 60 sec.), suggesting that the prolongation factor described above probably did not play an important role in causing higher rates of reactions with slower injections.

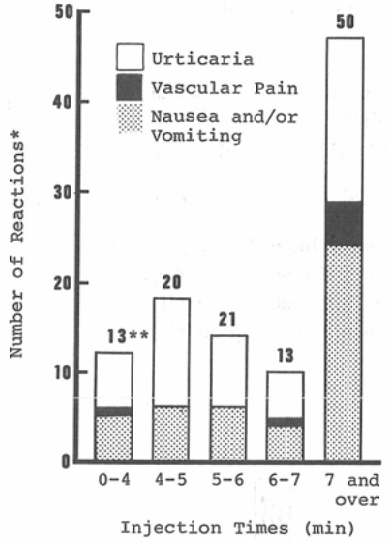

Fig. 5 Reactions according to injection times using drip infusions of mixtures of meglumine amidotrizoate and sodium amidotrizoate or meglumine iodamide.

*Some patients experienced more than one reaction.
**Total number of patients with reactions

There have been no previous reports of a statistically significant differeces in the incidence of nausea and/or vomiting and vascular pain according to injection times. Probably, there are etiological differences in these two groups of reactions. Haymarker and Kuhlenbeck reported that the most probable reason for vomiting was stimulation of the chemoreceptor trigger zone in the floor of the fourth ventricle, which controls the vomiting center. This zone is immediately adjacent to the area postrema, a region known for its lack of a blood-brain barrier (16). Lalli stated that the rapid onset of nausea and vomiting during or immediately following injections of contrast media are due to penetration of the area postrema and stimulation of the vomiting center (17). This is a function of contact time, anions and dosage, as contrast media penetrate the blood-brain barrier (18-20). Our administration of sodium iothalamate with its higher sodium content was accompanied by higher rates of reactions than the methylglucamine group (15). Sodium salts of various contrast media were considered more toxic for the brain than was methylglucamine (17). In all of these observations it appears that with bolus injections of sodium iothalamate, the relationship between injection times and acute reactions to the contrast medium is different from those of other groups of media. This was true in our series (Fig. 2, Table I and Fig. 4). Thus, at least part of the cause of nausea and/or vomiting is the concentration of the contrast medium (sodium iothalamate), and the chemotoxicity or hypertonicity.

As proved by post-injection radiography of injection sites (21), the vascular pain was due to vaso-spasm with stasis of the contrast medium. The cause of the vasospasm is a reflex action in response to irritation by the substance injected (22). This opinion is supported by the fact that the pain is localized in nature and rapid in onset. The irritation by the substance is the result of

hypertonicity or chemotoxicity. If so, vascular pain should be more frequent with rapid injections, which are accompanied by more hypertonic or chemotoxic effects. The results of our series did not agree with the incidence of vascular pain being lower with relatively rapid injections, possibly because rapid injections could increase the hyperosmolarity and chemotoxicity in the local vein. However, rapid injection expands the venous lumen, preventing vaso-spasm and vascular pain.

Urticaria stems from a different cause than does nausea and/or vomiting or vascular pain, because of the differences in relationships between injection times and these reactions to contrast media. There was no significant difference in the incidence of urticaria according to injection times by bolus injection or drip infusion. The incidence of urticaria was lower with the administration of sodium iothalamate than with other contrast media, but the rates of the other two major reactions were higher with bolus injections than drip infusions. From these observations it appears that urticaria is not due to the plasma concentration of the contrast material. Drip infusions are of longer duration than bolus injections, and they cause patients to feel unpleasant longer and to have greater anxiety.

Conclusions

The types of contrast media, severity of reactions to contrast media, the clinical efficacy, and ease of management of contrast media reactions were not compared in this study. Nor was a relatively "safe" or "safer" injection time determind. However, this series did show that there is no such "safe" injection time for drip infusions of mixtures of meglumine amidotrizoate and sodium amidotrizoate; that injection times longer than 81 seconds had a higher incidence of reactions than did rapid injections using bolus injections of sodium iothalamate; that the incidence of nausea and/or vomiting was lower in the group with injection times of 81 to 100 sec.; and that the frequency of vascular pain was lower with injections performed in 1 to 20 seconds and 41 to 60 seconds, than in other groups. The cause of urticaria is different from that of nausea and/or vomiting and vascular pain.

All radiologists utilizing excretory urography and contrast enhancement in computed tomography should be aware of these differences, especially when using bolus injections of contrast media.

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